IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Commissioner of Patents & Trademarks
Washington, D.C. 20231
Attn: Box Patent Application

Docket No. **SCH-1664-C1**
Prior Application: 09/242,334
Examiner: B. Trinh
Art Unit: 1612

Sir: This is a request for filing a
■ Continuation
□ Divisional
Under 37 C.F.R. 1.53(b), of prior application Serial No. **09/242,334** filed on **February 11, 1999** of **Jorg-Thorsten MOHR et al.**, for **PROCESS FOR PRODUCING OF DROSPIRENONE (6β, 7β, 15β, 16β-DIMETHYLENE-3-OXO-17α-PREGN-4-EN-21, 17-CARBOLACTONE, DRSP) AS WELL AS 7α-(3-HYDROXY-1-PROPYL)-6β, 7β; 15β, 16β-DIMETHYLENE-5β-ANDROSTANE-3β,5,17β-TRIOL (ZK 92836) AND 6β, 7β; 15β, 16β-DIMETHYLENE-5β-HYDROXY-3-OXO-17α-ANDROSTANE-21,17-CARBOLACTONE (90965) AS INTERMEDIATE PRODUCTS OF THE PROCESS**

1. ■ Enclosed are **eighteen (18)** pages of the specification including claims and **zero (0)** sheets of drawings.
2. ■ Enclosed is a copy of the oath or declaration as originally filed in Serial No. **09/242,334** on **February 11, 1999** in accordance with 37 C.F.R. §1.63(d).
3. ■ The filing fee is calculated below:

FOR	NUMBER FILED	NUMBER EXTRA	RATE	FEE
TOTAL CLAIMS	3 - 20	0	$18	0.00
INDEPENDENT CLAIMS	3 - 3	0	$78	0.00
□ MULTIPLE DEPENDENT CLAIM PRESENTED				
□ Small Entity Status Claimed under 37 CFR 1.9 and 1.27			BASIC FEE	690.00
Statement(s): □ Attached □ Filed in Parent			TOTAL FILING FEE	$690.00

4. ■ The amount of $**690.00** is included in the attached check.
   ■ If a check is not attached, authorization is given to charge the amount indicated in the above sentence to Deposit Account No. 13-3402; two copies of this page being attached for this purpose.
5. □ Please charge my Deposit Account No. 13-3402 in the amount of $_____, two copies of this sheet are attached.
6. ■ The Commissioner is hereby authorized to charge any deficiencies or credit any overpayment in payment of the following fees associated with this communication or otherwise due during the pendency of this application to Deposit Account No. 13-3402.
   ■ Any filing fees under 37 CFR §1.16 for the presentation of extra claims.
   ■ Any patent application processing fees under 37 CFR §1.17.
7. □ Cancel in this application original claims _____ of the prior application before calculating the filing fee.
8. ■ Amend the specification by inserting before the first line the sentence:
   -- This is a continuation of application Serial No. **09/242,334** filed **February 11, 1999**. --
9. ■ Priority of application No. **196 33 685.6** filed on **August 12, 1996** in **Germany** is claimed under 35 U.S.C. §119.
10. ■ The certified copies have been filed in prior application Serial No. **09/242,334** filed **February 11, 1999**.
11. ■ The prior application is assigned of record to **Schering AG** of **Berlin, Germany**.
12. ■ The power of attorney in the prior application is to: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B Shubin (32,004); Brion P. Heaney (32,542); Diana Hamlet-King (33,302); Richard J. Traverso (30,595); Richard E. Kurtz (33,936); John A. Sopp (33,103); John H. Thomas (33,460); Richard M. Lebovitz (37,067) and Luan C. Do (38,434)
    ■ a. The power appears in the original papers in the prior application.
    ■ b. Address all future communications to MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
13. ■ Incorporation By Reference.
    The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 2, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

Date: **August 18, 2000**

Anthony J. Zelano, Reg. No. 27,969- Attorney of Record
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 243-6333

AJZ/tal:K:\PAT\Sch\1664c1\Application Transmittal.wpd

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION

International Office

INTERNATIONAL APPLICATION PUBLISHED ACCORDING TO THE PATENT COOPERATION TREATY (PCT)

(51) International patent classification[6]: C07J 53/00 A1

(11) International publication number: WO 98/06738

(43) International publication date: February 19, 1998 (2/19/98)

(21) International file number: PCT/EP97/04342

(22) International application date: August 11, 1997 (8/11/97)

(30) Priority data: 196 33 685.6 August 12, 1996 (8/12/96) DE

(71) Applicant (for all designated countries except US):

SCHERING AKTIENGESELLSCHAFT [DE/DE]; Patents, Müllerstrasse 178, P. O. Box 65 03 11, D-13342 Berlin (DE).

(72) Inventors; and

(75) Inventors/applicants (only for US):

MOHR, Jörg-Thorsten [DE/DE]; Zwinglistrasse 4, D-10555 Berlin (DE). NICKISCH, Klaus [DE/DE]; Zescher Strasse 14, D-12307 Berlin (DE).

(74) Joint Representative: SCHERING AKTIENGESELLSCHAFT, Patents, Müllerstrasse 178, P. O. Box 65 03 11, D-13342 Berlin (DE).

(81) Designated countries: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG, ZU), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

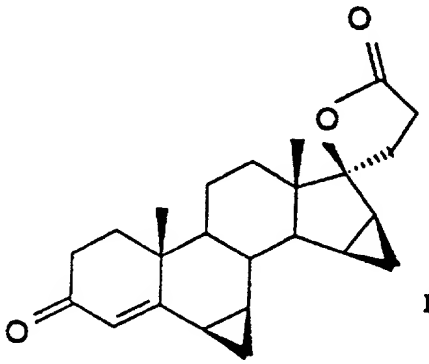
Published:

With international search report.

(54) **Title: PROCESS FOR THE PRODUCTION OF DROSPIRENONE (6ß,7ß; 15ß,16ß-DIMETHYLENE-3-OXO-17α-PREGN-4-ENE-21,17-CARBOLACTONE, DRSP) AND 7α-(3-HYDROXY-1-PROPYL)-6ß,7ß; 15ß,16ß-DIMETHYLENE-5ß-ANDROSTANE-3ß,5,17ß-TRIOL (ZK [CENTRAL CATALOG] 92836) AND 6ß,7ß; 15ß,16ß-DIMETHYLENE**

(57) **Abstract**

Process for the production of drospirenone (6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, DRSP) (1) and 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836) and 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (ZK 90965) as intermediate products of the process.



DRSP (I)

FOR INFORMATION ONLY

Codes used for identifying PCT member countries on the head sheets of the publications of international applications according to the PCT.

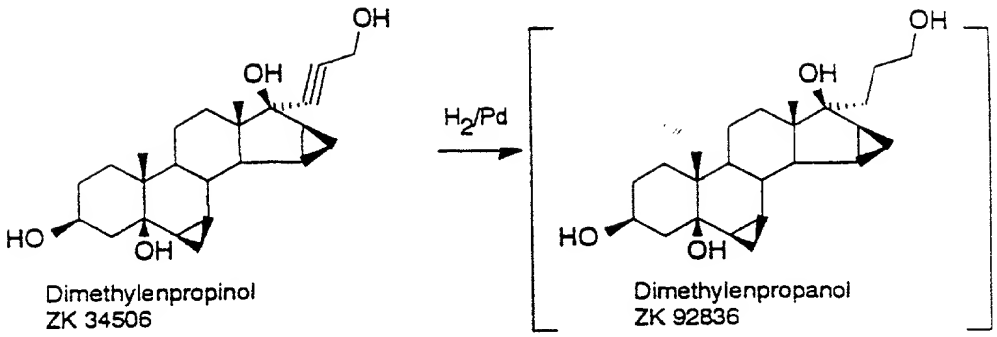
AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Ivory Coast
CM	Cameroon
CN	China
CU	Cuba
CZ	The Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greenland
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan

KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazachstan
LC	St. Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	the former Yugoslavian Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	The Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakian Republic
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	The Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Vietnam
YU	Yugoslavia
ZW	Zimbabwe

Process for the Production of Drospirenone (6ß,7ß; 15ß,16ß-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, DRSP) and 7α-(3-Hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836) and 6ß,7ß; 15ß,16ß-Dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (90965) as Intermediate Products of the Process.

The invention relates to a process for the production of drospirenone (6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, DRSP) and 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836) and 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (ZK 90965) as intermediate products of the process.

Drospirenone (6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, DRSP, INN) has been known for some time as a steroidal active ingredient (DE 26 52 761 C2 and DE 30 22 337 A1), and the production of the last 4 steps is carried out in a single-pot reaction; in which after dimethylene propinol ZK 34506 is hydrogenated, none of the intermediate stages dimethylene propanol and 5-ß-OH-DRSP that are passed through are isolated (see diagram below).

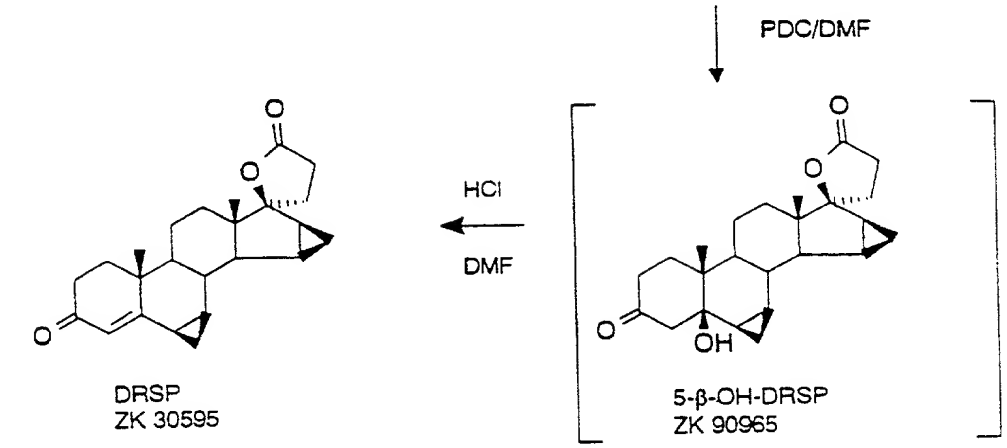


Dimethylene propinol

ZK 34506

Dimethylene propanol

ZK 92836



DRSP

ZK 30595

5-ß-OH-DRSP

ZK 90965

The dimethylene propinol ZK 34506 is hydrogenated in tetrahydrofuran with hydrogen on palladium-carbon into dimethylene propanol ZK 92836. The hydrogenating solution that is thus obtained, which contains propanol ZK 92836 as the main product and varying proportions of lactol, is reacted without

isolation and intermediate working-up to drospirenone ZK 30595 (DRSP).

For this purpose, a change of solvent from tetrahydrofuran to dimethylformamide first takes place and then the propanol is oxidized at 40°C with an excess of 3.7 equivalents of pyridinium dichromate (PDC) to a mixture of DRSP and 5-β-OH-DRSP. The 5-β-OH group in the oxidation product is labile compared to acids, Lewis acids and basic conditions at elevated temperatures, since in all cases, a more thermodynamically stable product is obtained with the formation of the Δ-4,5-unsaturated ketone in the drospirenone. The elimination of the β-OH group in the 5-β-OH-DRSP results in more thermodynamically stable drospirenone, and it was not possible to suppress it.

The mixture generally contains differing proportions of the two components, whereby 5-β-OH-DRSP is generally present as a main component at a ratio of 2-3:1. In the last stage of the single-pot sequence, the two-component mixture is converted by adding semi-concentrated hydrochloric acid into the DRSP, crude.

In the table below, the last four operating preparations are summarized.

Preparation	Yield, crude (%)	Purity (100% Method)
537201	57.2	98.9
202	63.7	99.09
203	46.5	99.18
204	58.3	98.81
Total	**Mean Yield: 56.4**	**Mean Purity: 98.9**

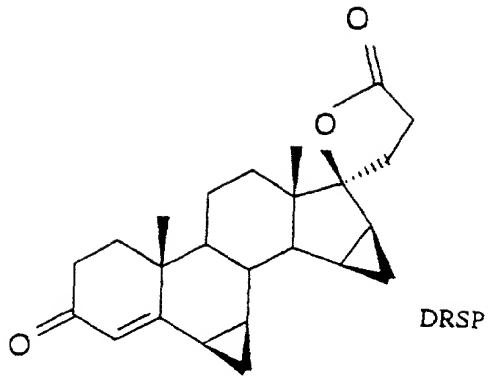
By the means of all operational preparations, starting from dimethylene propinol, a theoretical yield of 56% DRSP, crude at an HPLC purity of 98.9%, is achieved.

The object of the invention is the provision of a new production process for drospirenone, which is more selective and simpler in execution than that from the prior art and, in addition, is ecological (savings of a chromium trioxide oxidation).

This object is achieved according to the teaching of the claims.

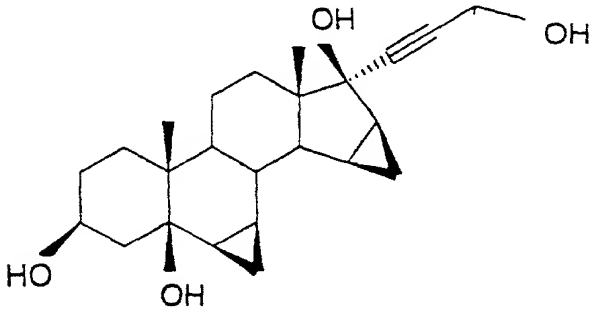
The invention contains a process for the production of drospirenone (6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-

21,17-carbolactone, DRSP)



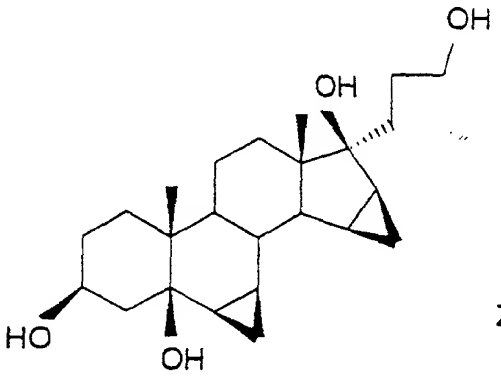
DRSP

by catalytic hydrogenation of 17α-(3-hydroxy-1-propynyl)-6ß,7ß; 15ß,16ß-dimethylene-5-androstane-3ß,5,17ß-triol (ZK 34506)



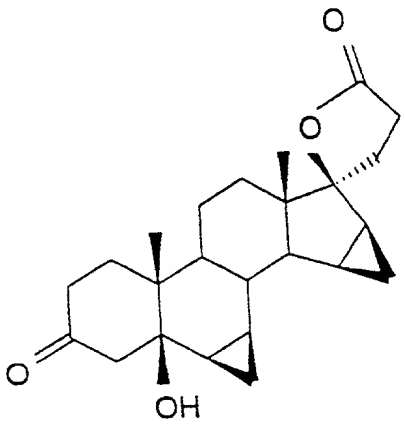
ZK 34506

into 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836)



ZK 92836

then oxidation with use of commercially available ruthenium salts, such as $RuCl_3$, RuO_2, $KRuO_4$, K_2RuO_4, but preferably in the presence of catalytic amounts of $RuCl_3$ (1 mol%) and conventional, simple oxidizing agents such as ^{t}butyl hydroperoxide, N-methyl-morpholine-N-oxide, $M_2S_2O_8$ (M = Na, K), MXOy (M = Li, Na, K; X = B, Cl, Br, 1: y = 1-4), but preferably 1-3 equivalents of $NaBrO_3$, in solvents such as acetonitrile, chloroform, methylene chloride, carbon tetrachloride, water, tetrahydrofuran, tert-butanol, ethyl acetate or combinations thereof, but preferably in an acetonitrile-water mixture in the composition of acetonitrile:water = 1:1, in 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (ZK 90965)



ZK 90965

and subsequent dehydration.

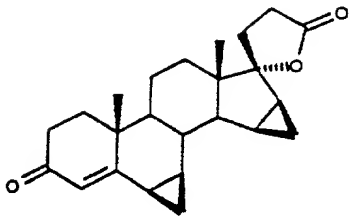
As a key reaction, the invention contains the ruthenium-catalyzed oxidation of dimethylene propanol ZK 92836 to 5-ß-OH-DRSP ZK 90965 and the subsequent elimination of water to drospirenone ZK 30595 in a two-stage process.

Analogously to the known process from the prior art, in the process according to the invention, dimethylene propinol ZK 34506 is hydrogenated with hydrogen on palladium-carbon into tetrahydrofuran. The hydrogenating solution is then subjected to a change of solvent, from tetrahydrofuran to acetonitrile. The acetonitrile solution is oxidized with a catalytic amount of ruthenium trichloride (1 mol%) and 3 equivalents of sodium bromate at 40°-60°C, specifically to 5-ß-OH-DRSP. Despite the significant lability of 5-ß-OH-DRSP compared to acids, Lewis acids, such as, for example, chromium compounds in old operating processes, strong bases or high temperatures, which in all cases can be attributed to the high driving force to form the more thermodynamically stable Δ-4,5-unsaturated ketone, the selective synthesis of 5-ß-OH-DRSP can be accomplished under the selected reaction conditions without a formation of drospirenone being observed. The 5-ß-OH-DRSP can be isolated from the reaction solution by a precipitation of water that is simple to implement (operationally).

The yields are in the range of 68% to 75% via the two stages: hydrogenation and then oxidation.

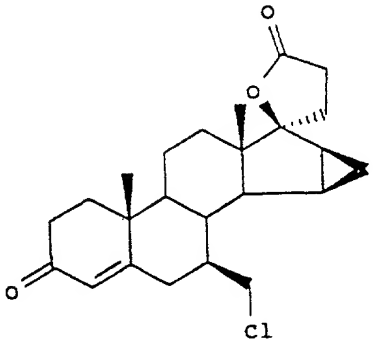
From some tests, it is known that in the case of acidic action, drospirenone can be decomposed with acidic action via two reaction routes. For one thing, under acidic conditions, the

drospirenone is easily converted into epimeric isolactone ZK 35096.



ZK 35096

The second by-product is produced by an HCl attack on the 6,7-methylene group, which results in ring opening product ZK 95673.



ZK 95673

Both by-products are pushed back under the reaction conditions of the new process to the extent that they can be observed only on an order of magnitude of < 0.2%.

In the elimination, a yield of 96% of theory is achieved. The total yield of the new process thus lies in the range of 65% to 72% of theory.

Another very basic advantage of the process according to the invention compared to the prior art lies in the range of ecology. It has been possible to replace the previously used toxic chromium compounds, which so far have been used in the form of pyridinium dichromate salts for oxidation and must subsequently be disposed of in the form of their solutions, by catalytic amounts of a metal. In addition, it is possible to recycle the used acetonitrile-water mixture by azeotropic distillation, so that also no danger to the environment is likely.

The invention also contains the intermediate products 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836) and 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (90965).

Examples:

6ß,7ß; 15ß,16ß-Dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone

50 g of 17α-(3-hydroxy-1-propynyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol is hydrogenated into 1000 ml of THF in the presence of 10 g of palladium on carbon (10%) and 3 ml of pyridine until 2 equivalents of hydrogen are taken up. Then, the catalyst is filtered off, and the solution is evaporated to the dry state, whereby 52.7 g of 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol is obtained, which is further reacted without purification.

50.2 g of 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol is suspended in 250 ml of acetonitrile and heated to 45°C. 0.52 g of ruthenium trichloride, dissolved in 10 ml of water, and 62.46 g of sodium bromate, dissolved in 250 ml of water, are added in drops to the above. It is stirred for 2 more hours at 50°C, and the solution is then quenched by adding 1000 ml of water. 200 ml of ethyl acetate is added, the phases are separated and then the aqueous phase is extracted with 600 ml of ethyl acetate. The combined organic phases are dried on sodium sulfate and then evaporated to the dry state. In this case, 43.44 g of 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone is obtained as crude product. 35.7 g of 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone with a melting

point of 216°-218°C is obtained by recrystallization from acetone-isoether. The rotation is approximately -65.6°C (sodium line, c = 1.02 in CHCl3).

6ß,7ß; 15ß,16ß-Dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone

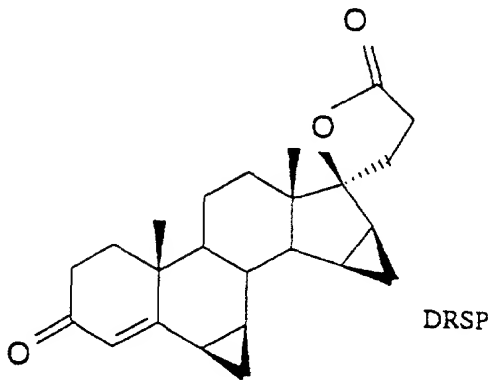
28 g of 6ß,7ß; 15ß,16ß-dimethylene-5ß-hydroxy-3-oxo-17α-androstane-21,17-carbolactone is suspended in 280 ml of THF and then mixed with 10 mol% of 1.5 g of p-toluenesulfonic acid. After 30 minutes, 125 ml of saturated NaCl solution and 8.2 ml of 1N NaOH solution are added. After phase separation, the organic phase is dried on sodium sulfate and evaporated to the dry state, whereby 25.67 g of 6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone is obtained as crude product, whose purity is approximately 93% according to HPLC determination.

Further purification can be done by chromatography.

The melting point of the chromatographed substance is approximately 197.5°-200°C.

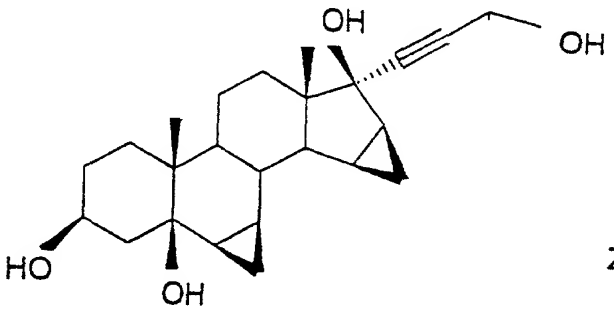
Claims

1. Process for the production of drospirenone (6ß,7ß; 15ß,16ß-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone, DRSP)



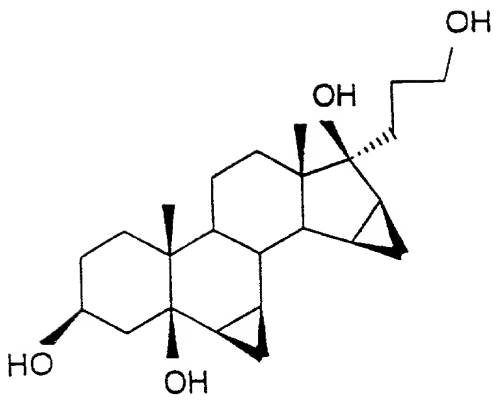
DRSP

by catalytic hydrogenation of 17α-(3-hydroxy-1-propynyl)-6ß,7ß; 15ß,16ß-dimethylene-5-androstane-3ß,5,17ß-triol (ZK 34506)



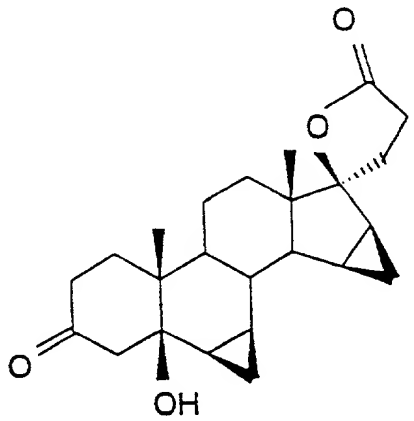
ZK 34506

into 7α-(3-hydroxy-1-propyl)-6ß,7ß; 15ß,16ß-dimethylene-5ß-androstane-3ß,5,17ß-triol (ZK 92836),



ZK 92836

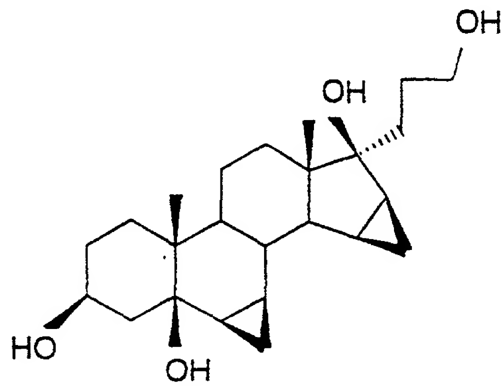
oxidation in the presence of a ruthenium salt into 6ß,7ß; 15ß,16ß-dimethylene-5α-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (ZK 90965)



ZK 90965

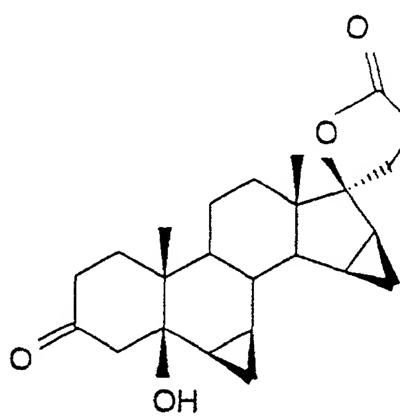
and subsequent dehydration.

2. 7α-(3-Hydroxy-1-propyl)-6β,7β; 15β,16β-dimethylene-5β-androstane-3β,5,17β-triol (<u>ZK 92836</u>)



ZK 92836

3. 6β,7β; 15β,16β-Dimethylene-5β-hydroxy-3-oxo-17α-androstane-21,17-carbolactone (<u>ZK 90965</u>)



ZK 90965

Docket No.
SCH 1664

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
PROCESS FOR PRODUCING DROSPIRENONE (6β, 7β; 15β, 16β-DIMETHYLENE-3-OXO-17α-PREGN-4-EN-21,17-CARBOLACTONE, DRSP), AS WELL AS 7α-(3-HYDROXY-1-PROPYL)-6β, 7β; 15β, 16β-DIMETHYLENE-5β-ANDROSTANE-3β, 5, 17β-TRIOL (ZK 92836) AND 6β, 7β; 15β, 16β-DIMETHYLENE-5β HYDROXY-5-OXO-17α-ANDROSTANE-21, 17-CARBOLACTONE

the specification of which

(check one)
☐ is attached hereto.
☒ was filed on 11 August 1997 as United States Application No. or PCT International Application Number PCT/EP97/04342
and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
196 33 685.6	Germany	12 August 1996	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

I. William Millen (Reg. No. 19,544)
John L. White (Reg. No. 17,746)
Anthony J. Zelano (Reg. No. 27,969)
Alan E.J. Branigan (Reg. No. 20,565)
John R. Moses (Reg. No. 24,983)
Harry B. Shubin (Reg. No. 32,004)
Brion P. Heaney (Reg. No. 32,542)
Richard J. Traverso (Reg. No. 30,595)
Diana Hamlet-King (Reg. No. 33,302)
John A. Sopp (Reg. No. 33,103)
Richard E. Kurtz (Reg. No. 33,936)
Richard M. Lebovitz (Reg. No. 37,067)
John H. Thomas (Reg. No. 33,460)
Luan Cao Do (Reg. No. 38,434)

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon Blvd., Suite 1400
Arlington, VA 22201

Direct Telephone Calls to: *(name and telephone number)*
Anthony J. Zelano (703-812-5311)

Full name of sole or first inventor
Jörg-Thorsten MOHR

Sole or first inventor's signature J. Mohr Date 17.12.98

Residence
Berlin, Germany

Citizenship
Germany

Post Office Address
Zwinglistrasse 4

D-10555 Berlin, Germany

Full name of second inventor, if any
Klaus NICKISCH

Second inventor's signature K. Nickisch Date 18.12.98

Residence
Berlin, Germany

Citizenship
Germany

Post Office Address
Zescher Strasse 14

D-12307 Berlin, Germany